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ORIGINAL PAPER

# Long-term results after PCI of unprotected distal left main coronary artery stenosis: the Bifurcations Bad Krozingen (BBK)-Left Main Registry

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## Abstract

**Aims** Percutaneous coronary intervention (PCI) of unprotected distal left main stenosis (UDLM) is increasingly performed as an alternative to surgical treatment. The optimal strategy for stenting in this setting is still a matter of debate. Therefore, this analysis investigated the long-term clinical outcome of a single- versus a double-stenting strategy for treatment of UDLM.

**Methods and results** From a large registry, 867 consecutive patients with UDLM undergoing either single or double stenting with drug-eluting stents (DES) were identified. Follow-up was up to 10 (median 3.1, interquartile range 1.1–5.3) years. Primary endpoint was MACE consisting of all-cause death, myocardial infarction, or target lesion re-intervention (TLR). Secondary clinical endpoints included these single endpoints and stent thrombosis. MACE occurred in 41.5% after single and in 49.0% after double stenting ($P=0.03$). TLR was lower after single (17.4%) as compared to double stenting (27.2%; $P<0.01$). Between single and double stenting, there were no significant differences for death (26.4 versus 23.3%; $P=0.31$), death or myocardial infarction (29.1 versus 27.2%; $P=0.55$), or definite/probable stent thrombosis (1.3 versus 2.1%; $P=0.42$).

**Conclusions** Compared with single stenting, double stenting was associated with a significantly higher long-term risk of MACE. This was driven by a higher incidence of TLR, whereas the risk of death, MI, or stent thrombosis was similar between the two strategies.

**Keywords** Distal left main stenosis · Bifurcation · TAP stenting · Drug-eluting stents · Restenosis · Reintervention

## Introduction

Percutaneous coronary intervention (PCI) of patients with unprotected left main stenosis (UDLM), mainly distal left main stenosis (>75%), was analysed in several large randomized trials [1–6]. According to the recommendations of the European Bifurcation Club (EBC) [7], single stenting followed by a final kissing balloon dilatation for the side branch should be the preferred PCI strategy for PCI of distal left main stenosis. During PCI of coronary bifurcation lesions (including distal left main stenosis), double stenting is required in 5–36% [8, 9] to achieve an optimal angiographic result. The recently published DKCRUSH-V trial showed that a routine strategy implanting two stents using the double-kissing crush technique is superior to an approach with provisional stenting of the side branch [4] during 1-year follow-up. In contrast to T-and-protrusion (TAP) and Culotte stenting enabling a provisional side branch approach, commitment to the more challenging DK (double kissing) crush technique must be made at the beginning of the procedure. Few registries [10–12] have demonstrated good short and intermediate clinical outcomes after PCI of distal left main stenosis using single- or double-stenting approaches. However, only limited data are available regarding long-term results up to 10 years after index PCI using only drug-eluting stents (DES) [13, 14].

In our Bifurcations Bad Krozingen (BBK) Registry, we analysed the long-term clinical outcomes of single versus double stenting for unprotected distal left main stenosis.

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## Methods

### Study population

For the current analysis, we included all consecutive patients of the BBK Registry who underwent PCI with DES for a de novo distal left main stenosis from January 2004 till December 2014. All patients had a pre-PCI history of angina, a positive stress test or presented with acute coronary syndrome (ACS). As part of the quality management program of our institution, baseline demographic, clinical, angiographic and procedural data as well as outcome data are entered into a database.

To be eligible for this analysis, patients had to have undergone successful PCI with DES placement of a de novo distal, unprotected left main bifurcation lesion of a native coronary artery with > 50% diameter stenosis of the main branch or the side branch. All included patients were treated with approved DES. Patients treated by PCI and DES during ongoing mechanical resuscitation were excluded from the analysis.

### Preparation, stenting procedure and follow-up

At least 2 h before the intervention, stable patients received a loading dose of 600 mg of clopidogrel. Patients with ACS were preloaded with either 600 mg clopidogrel, or 60 mg prasugrel or 180 mg ticagrelor. In the catheterization laboratory, we administered an intraarterial dose of 100 U/kg heparin plus intravenous aspirin, 500 mg, if the patient was not on chronic treatment with aspirin. Glycoprotein IIb/IIIa inhibitors were administered only in selected patients with ACS or in bail-out situations.

The choice of DES was left to the operator's discretion. Distal left main stenosis was treated according to the provisional side-branch stenting technique described earlier [9]. Treatment of the side branch was performed in case of the occurrence of the residual stenosis > 75%, dissections, or a TIMI flow < 2, by TAP- or Culotte-stenting technique according to the coronary anatomy and/or operator's choice [9].

Post-PCI, we recommended lifelong aspirin (≥ 100 mg per day) and clopidogrel (≥ 75 mg per day) or prasugrel or ticagrelor for 6 or 12 months.

As part of our routine follow-up, plasma concentrations of creatinine kinase (CK) and its isoenzyme, CK-MB, are systematically determined for 36 h after the intervention. In addition, we obtain at least two ECG recordings during that time. We also perform an interview at 1 year, and at 3 years after PCI. In addition, we contacted all patients in December 2015. The long-term follow-up was approved by the ethics committee of the medical faculty of the University of Freiburg, Germany.

### Medina classification and calcification score

By visual assessment, bifurcation lesions were characterized according to the Medina classification [15]. Estimation of degree of calcification in bifurcation lesions was visually assessed and classified as minimal (only minimal visual calcification), moderate (multiple visible sites of calcification) or severe calcification (severe homogeneous calcification in both branches including the area of the carina) [9].

### Clinical endpoints and definitions

The efficacy endpoint in this analysis was the cumulative incidence of major adverse cardiac events (MACE), comprising all-cause death, myocardial infarction and target lesion revascularization (TLR). As secondary endpoints, we investigated components of the primary endpoint and definite or probable stent thrombosis as defined by the ARC criteria [16]. Definition of events was used as described previously [9].

### Statistical methods

For statistical analyses, we used the SPSS software package, version 23 (SPSS Inc., Chicago, IL, USA). All tests were two sided and results were regarded as statistically significant at an $\alpha$ level of 5%. Discrete variables were reported as counts (percentages) and continuous variables as mean ± standard deviation. For discrete variables, we tested differences between groups with the $\chi^2$ test or Fisher's exact test when expected cell sizes were less than five. We used the two-tailed *t*-test to compare continuous variables. The incidence of clinical endpoints between the strata defined by stent type was compared by log-rank testing. Cumulative event rates were calculated and graphically described according to the Kaplan–Meier method. We further performed landmark analyses with short-term follow-up up to 1 year (0–1 year) and long-term follow-up thereafter (1–10 years). We derived hazard ratios (HR) with corresponding 95% confidence intervals (CI) from Cox proportional hazards models.

## Results

### Patient cohort

Between January 2004 and December 2014, we identified 867 consecutive patients with successful PCI of unprotected distal left main stenosis who met the selection criteria (Fig. 1). These patients were included in this analysis. Based

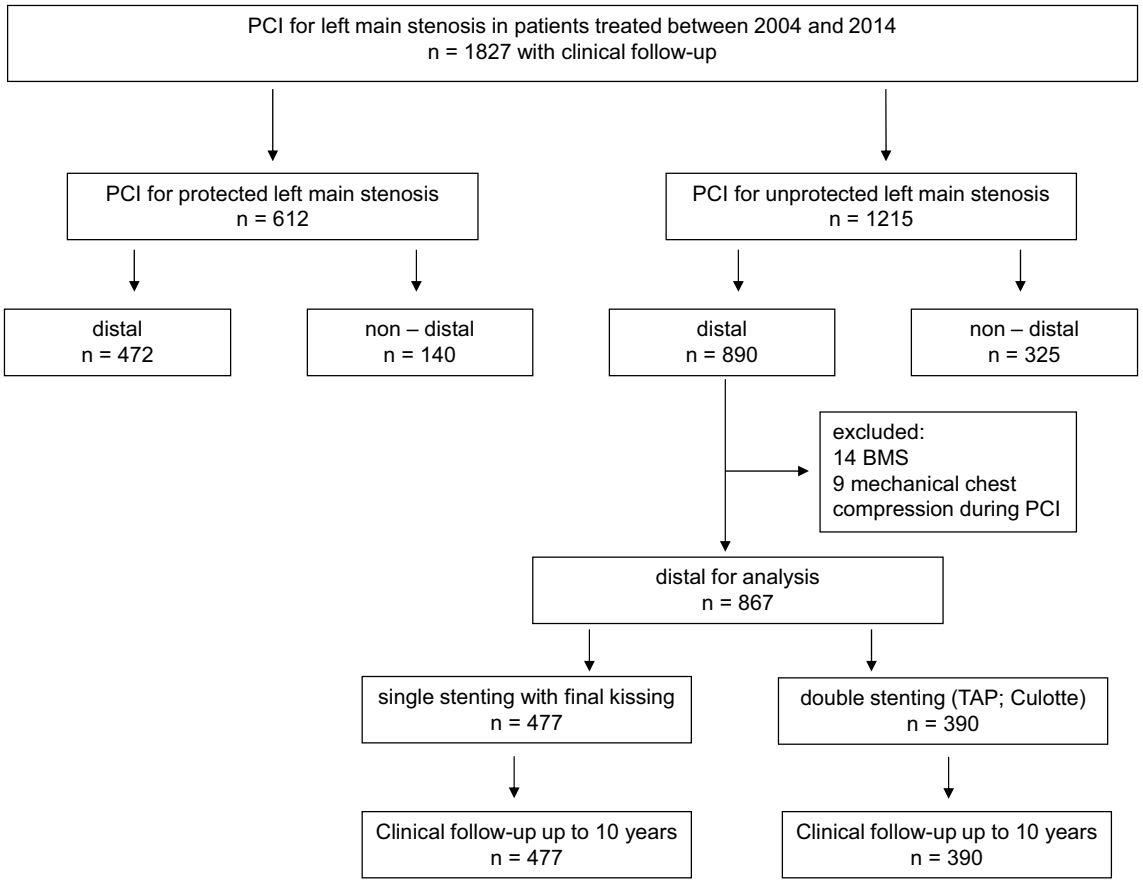


**Fig. 1** Study flowchart of the BBK-Left Main Registry

on the provisional side-branch stenting strategy, a stent in the side branch was needed in 390 (45%) patients to achieve an optimal final angiographic result.

Median follow-up was 3.1 (1.1–5.3) years with no significant difference between single and double stenting [3.3 (1.3–5.4) versus 3.0 (0.9–5.3) years, $P = 0.06$]. The mean age was 70.4 ± 10.8 years and 74.7% of patients were male. Patients presented with ACS in 27.4% of cases and diabetes mellitus was prevalent in 29% of the patients. Other demographic, angiographic, and procedural characteristics of the study population are summarized in Tables 1 and 2. True bifurcation lesions were significantly more frequent in the double-stenting group (83.3 versus 42.3%, $P < 0.01$). The rate of the severe calcifications was similar in both treatment groups (Table 2).

## Clinical outcomes for the entire follow-up period

Clinical endpoints are summarized in Table 3. The incidence of MACE was significantly lower following single stenting as compared to double stenting (HR 0.81; 95% CI 0.67–0.99; $P = 0.04$; Fig. 2a). MACE was mainly driven by significant differences in TLR over 10 years (HR 0.62; 95% CI 0.47–0.83; $P < 0.001$; Fig. 2b). The cumulative incidence of the composite of death or myocardial infarction was not significantly different (HR 1.12; 95% CI 0.86–1.44; $P = 0.40$; Fig. 2c). All-cause death was similar after 10 years of follow-up in both treatment groups (HR 1.18; 95% CI 0.90–1.55; $P = 0.22$; Fig. 2d). Definite/probable stent thrombosis (Table 3) was rare without significant differences between groups: 1.3% after single and in 2.1% after double stenting ($P = 0.42$).

After adjustment for angiographic variables with significant differences between both groups (true bifurcation lesion, pre-PCI stenosis of main and side branch, calcification score in LAD), there remained no significant differences in MACE between the two groups (HR 0.95; 95% CI 0.74–1.22; $P = 0.68$). Adjusted rates for TLR tended to be lower (HR 0.74; 95% CI 0.51–1.06; $P = 0.10$) whereas there was a trend towards higher mortality in the group with a single-stent strategy (HR 1.33; 95% CI 0.95–1.87; $P = 0.10$). For death or myocardial infarction, no significant differences between the groups were observed (HR 1.27; 95% CI 0.92–1.74; $P = 0.15$).

**Table 1** Baseline clinical characteristics

| | Single stenting ($n=477$) | Double stenting ($n=390$) | *P* |
|---|---|---|---|
| Age (years) | 70.6 ± 10.7 | 70.2 ± 10.9 | 0.59 |
| Male gender (%) | 357 (74.8%) | 291 (74.6%) | 0.94 |
| Diabetes mellitus (%) | 140 (29.4%) | 111 (28.5%) | 0.82 |
| Current smoker (%) | 56 (11.7%) | 48 (12.3%) | 0.83 |
| Hypertension (%) | 404 (84.7%) | 326 (83.6%) | 0.71 |
| Family history (%) | 146 (30.6%) | 135 (34.6%) | 0.22 |
| Cholesterol (mg/dL) | 181 ± 46 | 184 ± 45 | 0.28 |
| LDL cholesterol (mg/dL) | 112 ± 41 | 115 ± 40 | 0.21 |
| Serum creatinine (mg/dL) | 1.16 ± 0.83 | 1.14 ± 0.87 | 0.79 |
| C-reactive protein (mg/dL) | 1.18 ± 2.87 | 1.13 ± 3.0 | 0.79 |
| Haemoglobin (g/dl) | 13.6 ± 1.8 | 13.8 ± 1.7 | 0.06 |
| History of MI (%) | 124 (26.0%) | 92 (23.6%) | 0.43 |
| History of PCI (%) | 155 (32.5%) | 111 (28.5%) | 0.21 |
| History of CABG (%) | 0 (0.0%) | 0 (0.0%) | |
| Left ventricular ejection fraction (%) | 48 ± 9.7 | 49 ± 0.9.2 | 0.07 |
| Acute coronary syndrome (%) | 135 (28.3%) | 103 (26.4%) | 0.54 |

*LDL* low-density lipoprotein, *MI* myocardial infarction, *PCI* percutaneous coronary intervention, *CABG* coronary artery bypass grafting

### Clinical outcomes for short- and long-term follow-up periods

Landmark analyses showed that MACE was only significantly different within the short-term follow-up up to 1 year (HR 0.69; 95% CI 0.52–0.91; $P=0.01$). Within the long-term follow-up, no significant differences in MACE were detectable (HR 0.96; 95% CI 0.72–1.27; $P=0.78$) (Fig. 3a). In terms of TLR, there was a significantly lower rate in both short- and long-term follow-up in the single-stenting group ($P=0.01$, respectively $P=0.04$) (Fig. 3b). In contrast, death and rates of myocardial infarction were not significantly different during the first year after PCI ($P=0.47$). However, during subsequent follow-up, double stenting was associated with a trend towards lower event rates ($P=0.11$) (Fig. 3c). All-cause death occurred at similar rates during the first year of follow-up ($P=0.90$). After 1 year, there were numerically lower rates of death in the double-stenting group ($P=0.16$) (Fig. 3d).

## Discussion

This analysis of the BBK-Left Main Registry investigates the long-term clinical outcomes after PCI of the de novo unprotected distal left main stenosis using single or double stenting. The key message is threefold: (1) single stenting using DES was associated with significantly lower risk of MACE than double stenting, driven by lower rate of TLR, (2) the stenting technique did not significantly modify the risks of death, MI or stent thrombosis and (3) the observed incidences for death and MI appeared more favourable for double stenting in landmark analyses beyond 1 year.

This study is exclusively focused on distal left main stenosis. An overall high rate of true bifurcations lesions (61%) was present. Furthermore, second- or third-generation DES were used in most patients (68%). Finally, long-term follow-up for up to 10 years was available for all included patients and enabled landmark analyses to gain insights into outcome differences between short- and long-term follow-up periods.

For treatment of unprotected left main disease, few studies and registries reported better outcomes after use of second- as compared to first-generation DES [14, 17]. In addition to newer generation stents, the TAP- and Culotte-stenting techniques that were used in the current study represent approaches with wide current use as compared to the techniques used in earlier studies [11, 18]. Also, according to the current guidelines [7], all patients with single stenting underwent a final kissing balloon dilatation of the side branch. Nevertheless, on the whole, the current findings are in line with data using first-generation DES [10]. Double stenting is still associated with higher TLR rates without a negative impact on mortality or the risk of myocardial infarction.

**Table 2** Baseline angiographic and procedural characteristics

| | Single stenting ($n=477$) | Double stenting ($n=390$) | $P$ |
|---|---|---|---|
| Number of vessels affected (%) | | | 0.61 |
| One vessel | 0 (0%) | 0 (0%) | |
| Two vessels | 154 (32.3%) | 119 (30.5%) | |
| Three vessels | 323 (67.7%) | 271 (69.5%) | |
| Distribution of bifurcation (%) | | | |
| Distal left main | 477 (100%) | 390 (100%) | |
| LCX as side branch | 345 (72.3%) | 275 (70.5%) | 0.60 |
| LAD as side branch | 132 (27.7%) | 115 (29.5%) | |
| True bifurcation lesions (111, 101, 011), *n* (%) | 202 (42.3%) | 325 (83.3%) | < 0.01 |
| Medina classification (%) | | | < 0.01 |
| 111 | 145 (30.4%) | 235 (60.3%) | |
| 110 | 161 (33.8%) | 31 (7.9%) | |
| 101 | 47 (9.9%) | 50 (12.8%) | |
| 100 | 68 (14.3%) | 11 (2.8%) | |
| 011 | 10 (2.1%) | 40 (10.3%) | |
| 010 | 39 (8.2%) | 9 (2.3%) | |
| 001 | 7 (1.5%) | 14 (3.6%) | |
| Calcifications in LCX (by visual estimation) | | | 0.08 |
| None | 34 (7.1%) | 19 (4.9%) | |
| Minor | 328 (68.8%) | 245 (62.8%) | |
| Moderate | 99 (20.8%) | 107 (27.4%) | |
| Severe | 16 (3.4%) | 19 (4.9%) | |
| Calcifications in LAD (by visual estimation) | | | 0.04 |
| None | 24 (5.0%) | 11 (2.8%) | |
| Minor | 324 (67.9%) | 246 (63.1%) | |
| Moderate | 109 (22.9%) | 113 (29%) | |
| Severe | 20 (4.2%) | 20 (5.1%) | |
| Double-stenting technique | | | |
| Culotte stenting | | 42 (10.8%) | |
| TAP stenting | | 348 (88.2%) | |
| Reason for double stenting (%) | | | |
| Dissection (%) | | 138 (35.4%) | |
| Residual stenosis > 75% | | 326 (83.6%) | |
| TIMI 0 or 1 (%) | | 11 (2.8%) | |
| According to the operator's decision | | 31 (7.9%) | |
| Contrast volume (mL) | 203 ± 145 | 244 ± 142 | < 0.01 |
| Fluoroscopy time (min) | 16 ± 14 | 21 ± 17 | < 0.01 |
| Radiation exposure ($\mu Gym^2$) | 6405 ± 7313 | 8037 ± 8846 | 0.03 |
| Use of anti-GPIIb/IIIa (abciximab) (%) | 13 (10.7%) | 19 (18.8%) | 0.09 |
| Maximal inflation pressure (atm) | | | |
| Main branch | 15.6 ± 3.7 | 15.8 ± 3.6 | 0.95 |
| Side branch | 14.4 ± 2.0 | 14.6 ± 1.8 | 0.16 |
| Stent diameter (mm) | | | |
| Main branch | 3.87 ± 1.2 | 3.83 ± 1.3 | 0.18 |
| Side branch | | 3.2 ± 0.36 | |
| First stent in the main branch, *n* (%) | | | 0.08 |
| Sirolimus (Cypher) | 75 (15.7%) | 91 (23.3%) | |
| Paclitaxel (Taxus) | 63 (13.2%) | 48 (12.3) | |
| Zotarolimus (Resolute; Res. Integrity) | 136 (28.5%) | 105 (26.9) | |
| Everolimus (Xience; Promus) | 185 (38.8%) | 132 (33.8%) | |

**Table 2** (continued)

| | Single stenting ($n=477$) | Double stenting ($n=390$) | *P* |
|---|---|---|---|
| Biodegradable polymer (Orsiro; Synergy) | 18 (3.8%) | 14 (3.6%) | |
| Second stent in the side branch, *n* (%) | | | |
| Sirolimus (Cypher) | | 86 (22.1%) | |
| Paclitaxel (Taxus) | | 45 (11.5%) | |
| Zotarolimus (Resolute; Resolute Integrity) | | 103 (26.4%) | |
| Everolimus (Xience; Promus) | | 144 (36.9%) | |
| Biodegradable polymer (Orsiro; Synergy) | | 12 (3.1%) | |

*LAD* left anterior descending coronary artery, *LCX* left circumflex coronary artery, *PCI* percutaneous coronary intervention, *DES* drug-eluting stent

**Table 3** Clinical outcome during 10 years after index-PCI

| | Single stenting ($n=477$) | Double stenting ($n=390$) | *P* |
|---|---|---|---|
| Death all cause (%) | 126 (26.4%) | 91 (23.3%) | 0.31 |
| Death—cardiac (%) | 60 (12.6%) | 39 (10.0%) | 0.49 |
| Death—non-cardiac (%) | 66 (13.8%) | 52 (13.3%) | 0.49 |
| Death or myocardial infarction (%) | 139 (29.1%) | 106 (27.2%) | 0.55 |
| Stent thrombosis any (%) | 28 (5.9%) | 18 (4.6%) | 0.45 |
| Definite (%) | 2 (0.4%) | 0 (0%) | 0.50 |
| Probable (%) | 4 (0.8%) | 8 (2.1%) | 0.15 |
| Possible (%) | 22 (4.6%) | 10 (2.6%) | 0.15 |
| Definite/probable (%) | 6 (1.3%) | 8 (2.1%) | 0.42 |
| Early (definite/probable) (%) | 6 (1.3%) | 6 (1.5%) | 0.28 |
| Late (definite/probable) (%) | 0 (0%) | 2 (0.5%) | 0.28 |
| TLR (%) | 83 (17.4%) | 106 (27.2%) | $<0.01$ |
| MACE (%) | 198 (41.5%) | 191 (49.0%) | 0.03 |

*TLR* target lesion revascularization, *MACE* major cardiac adverse events

In contrast to our study, Gao et al. [19] reported comparable rates of MACE after single and double stenting for unprotected distal left main stenosis. Even in multivariate analysis, the double stenting technique was not predictive of MACE. In this study, the majority of patients was treated with crush technique (69%) and only few patients with T-stenting or Culotte stenting. Notably, the recent DKCRUSH-V trial demonstrated that, during a limited 1-year follow-up after PCI of left main bifurcation lesions, DK crush stenting was superior to a provisional stenting strategy in terms of target lesion failure as well as myocardial infarction and stent thrombosis [4].

Only limited data are currently available regarding longer periods of clinical follow-up. Here, the landmark analyses of our study provide additional evidence for the safety of a double-stenting strategy. Neither in the first year nor beyond 1 year after PCI double stenting was associated with any increase of myocardial infarction or all cause death.

## Limitations

A major limitation of our study is its non-randomized nature and retrospective analysis. Due to the non-randomized nature of our study, it remains unclear whether the higher need for TLR with double stenting was caused by a negative impact of this stenting technique or by the intrinsic properties of the lesion that necessitated the use of an additional stent.

Our registry applied provisional side-branch stenting as the uniform stenting technique. If side-branch stenting was needed, we performed only TAP and Culotte stenting. The DK-crush technique, which showed benefit over Culotte stenting [20], was not used in this patient cohort.

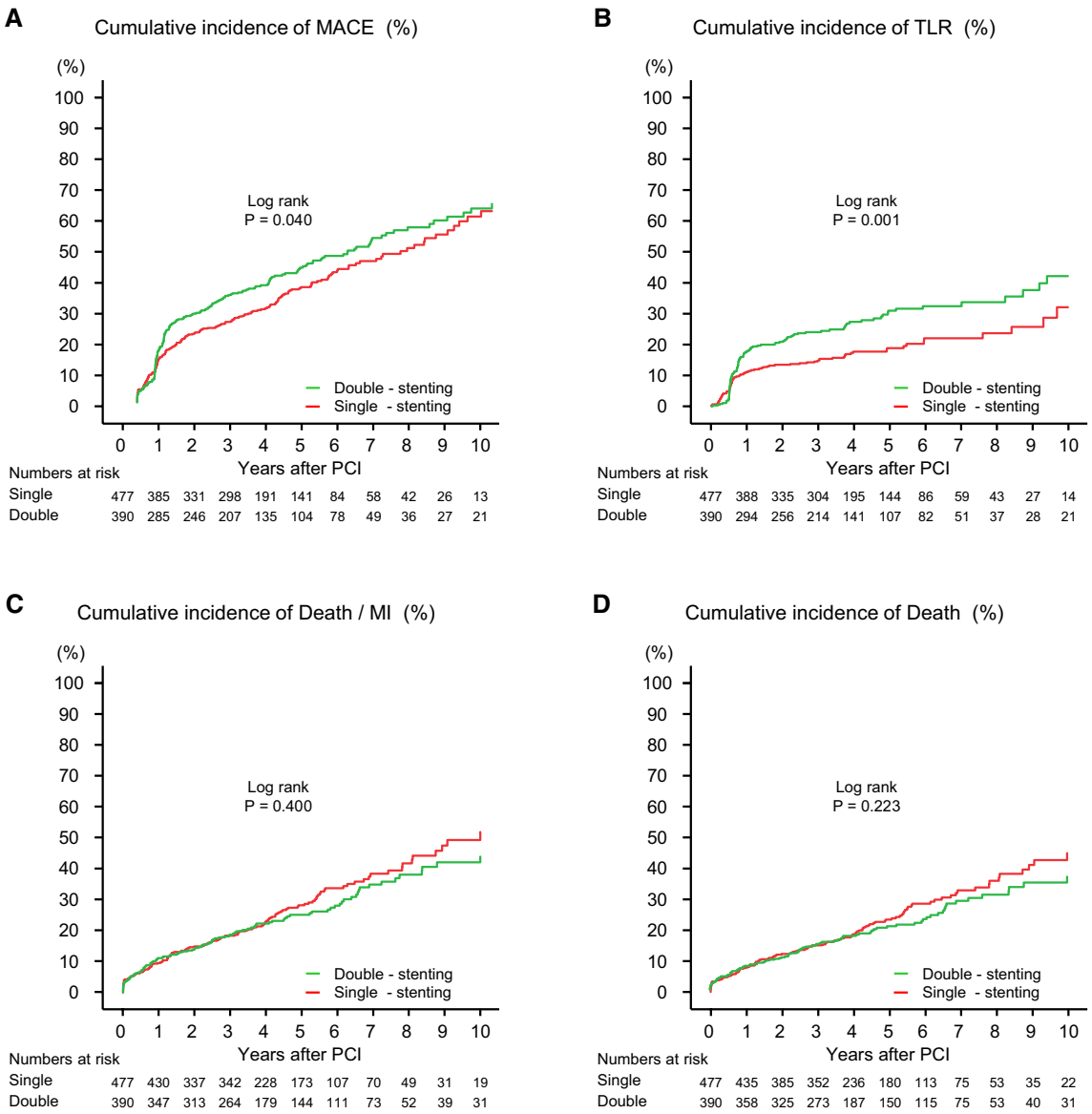


**Fig. 2** Analysis for the entire follow-up period. Non-adjusted Kaplan–Meier estimates for cumulative event rates of **a** MACE, **b** TLR, **c** death/MI and **d** all-cause death in patients with single stenting (red) or double stenting (green). *P* value by log-rank test

## Impact on daily practice

The results of this study, including patients with ACS, encourage treating patients with a provisional approach for side-branch stenting. If double stenting must be performed to achieve an optimal angiographic result, this study demonstrated no safety concerns for up to 10 years of clinical follow-up. The ongoing EBC-Main trial will be the first randomized trial investigating the optimal strategy for PCI of distal left main stenosis without preselecting a distinct technical approach for double stenting [21].

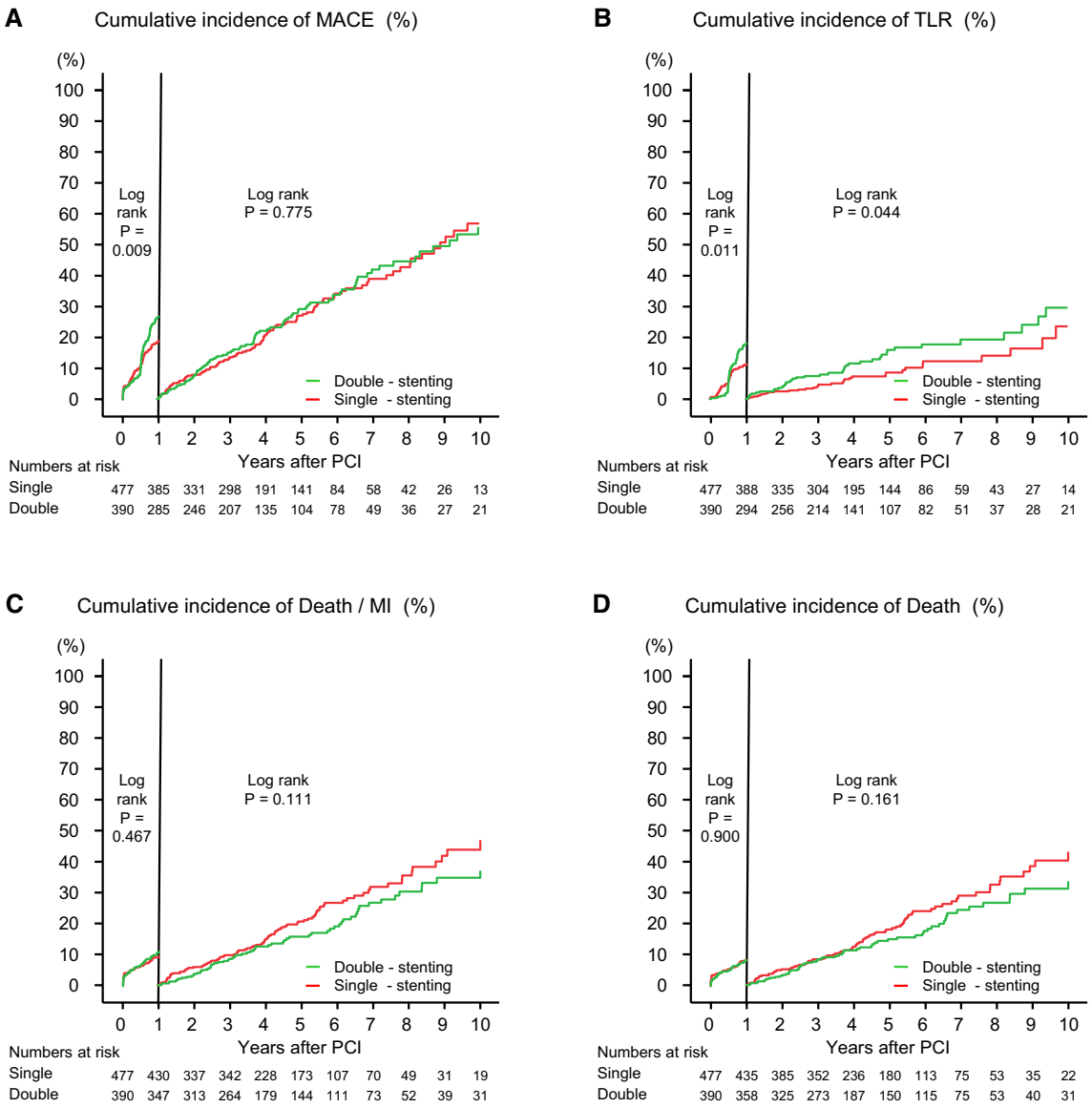


**Fig. 3** Landmark analysis for short-term and long-term follow-up periods. Non-adjusted Kaplan–Meier estimates for cumulative event rates of **a** MACE, **b** TLR, **c** death/MI and **d** all-cause death in patients with single stenting (red) or double stenting (green). Line at 1 year denotes separation between follow-up periods. *P* value by log-rank test

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## Compliance with ethical standards

**Conflict of interest** Dr. Ferenc received speaker honoraria from Abbott Vascular, Biotronik, Boston Scientific, Daiichi Sankyo, Medtronic and Terumo. Dr. Hochholzer reports receiving consulting and lecture fees from AstraZeneca, Boehringer Ingelheim, Daiichi Sankyo and the Medicines Company. Dr. Mashayekhi received consulting/speaker honoraria from Abbott Vascular, Asahi Intecc, Biotronik, Boston Scientific, Daiichi Sankyo, Nitiloop, Terumo and Vascular Solutions. The other authors report no conflicts of interest.

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